Gadoversetamide
Gd-DTPA-BMEA

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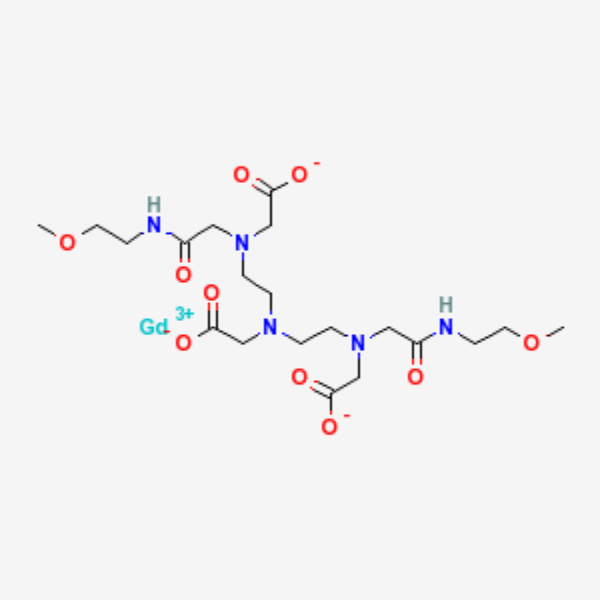
Chemical name: Gadoversetamide
Abbreviated name: Gd-DTPA-BMEA
Synonym: OptiMARK®
Backbone: Compound
Target: Central nervous system, liver
Mechanism: BBB breakage, liver pathologies with abnormal vascularity
Method of detection: MRI
Source of signal: Gadolinium
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: Yes
Non-human primate studies: No
Human studies: Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov/].

Background

[PubMed]

Gadoversetamide (Gd-DTPA-BMEA) is an intravenous, paramagnetic contrast agent of magnetic resonance imaging (MRI) developed for imaging of the central nervous system (CNS) and liver (1-3).

Paramagnetic contrast agents are generally metal chelates with unpaired electrons, and they work by shortening both T_1 and T_2 relaxation times of surrounding water protons to produce the signal-enhancing effect (4, 5). At normal clinical doses of 0.1-0.2 mmol/kg, the T_1 effect tends to dominate. Current agents are water-soluble compounds that do not cross the intact blood-brain barrier (BBB).They can be used to enhance signals of CNS tissues that lack a BBB (e.g., pituitary gland), extraaxial tumors (e.g., meningiomas) and areas of BBB breakdown (e.g., tumor margins). In these cases, small or multiple CNS lesions are more clearly delineated with contrast enhancement. In addition, contrast enhancement can highlight vasculature, delineate the extent of disease

and confirm the impression of normal or nonmalignant tissues. These contrast agents can also be used in a similar nonspecific manner to enhance contrast between normally perfused areas and pathologies with altered vascularity in the liver (6).

Gadolinium (Gd), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective at enhancing proton relaxation because of its high magnetic moment and very labile water coordination. Gadopentetate dimeglumine (Gd-DTPA) was the first intravenous MRI contrast agent used clinically, and a number of similar gadolinium chelates have been developed in an effort to further improve clinical efficacy, patient safety and patient tolerance. The major chemical differences among these Gd chelates are the presence or absence of overall charge, ionic or nonionic, and their ligand frameworks (linear or macrocyclic). DTPA-BMEA is a linear nonionic chelate developed as a bis(methoxyethylamide) derivative of DTPA. Being nonionic, Gd-DTPA-BMEA has a lower osmolality of 1110 mOsm/kg (Gd:solute ratio of 1:1) than Gd-DTPA (1940 mOsmo/kg).

The commercial formulation of Gd-DTPA-BMEA contains 330.9 mg of gadoversetamide/ml and has a pH of 5.5-7.5, viscosity of 2.0 cP at 37ºC, and density of 1.160 g/ml (1).

Synthesis

[PubMed]

DTPA-BMEA was synthesized by reacting the DTPA-bisanhydride with 2-methoxyethylamine at 50ºC for 4 h as reported by Weber (7, 8). The yield was 93.5%. DTPA-BMEA was then reacted with gadolinium(III) oxide at 60-65ºC for 3 h to produce Gd-DTPA-BMEA. The final yield was 80.7%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Rothermel and colleagues (7) used radioactive Eu(III) to study the metal exchange kinetics of Gd-DTPA-BMEA *in vitro* at 0.15 M ionic strength and 25ºC. They concluded that it had the same dissociative pathways as conventional aminocarboxylate systems, but the incorporation of the two bulky amide groups led to slower rates of formation and dissociation. The *invitro* $1/T_1$ nuclear magnetic relaxation dispersion (NMRD) profile of Gd-DTPA-BMEA was assessed in another study (9, 10). The water exchange rate (k_{ex}^{298}) was found to be $0.39 \pm 0.02 \times 10^6$ s^{-1} and the activation volume ($\Delta V\neq$) was 7.4 ± 0.4 cm^3 mol^{-1}. It also appeared to have a similar $1/T_1$ NMRD profile as Gd-DTPA at 35ºC. The T_1 and T_2 relaxation rates ($mM^{-1}sec^{-1}$) in water were reported to be 4.60 and 4.81, respectively

Some studies indicated that Gd-DTPA-BMEA could interfere with *in vitro* (Ca, Zn, and angiotensin-converting enzyme) colorimetric assays of patient samples (11-13). After continuous exposure to 2500 µg/ml of Gd-DTPA-BMEA in a toxicity study (14), numerical chromosome aberrations in Chinese hamester ovary cells were 5.0% and 3.5% at 24 h and 48 h, respectively. For 5000 µg/ml, the percentages were 6.3% and 22.5%. The results did not support *in vivo* clastogenic risk for Gd-DTPA-BMEA. Other tests of genetic toxicology (plate incorporation mutagenicity assay and mouse lymphoma mutagenesis assay) were negative.

Animal Studies

Rodents

[PubMed]

The acute LD_{50}s for i.v. (mice) and intracisternal (rats) administrations of Gd-DTPA-BMEA were reported to be 25-28 and 0.166 mmol/kg, respectively (14). No repeated-dose toxicity in rats was observed with daily administration of 0.1 mmol/kg for 28 days. Some non-lethal changes were observed with the higher chronic doses of 0.6-3 mmol/kg. In a study of the local tissue toxicity in response to extravascular extravasation, Gd-DTPA-BMEA showed similar reactions, but with less inflammation, as compared with Gd-DTPA (15). The micronucleus cytogenic assay in mice was negative. No effect was observed in reproductive toxicology tests in rats at doses of 0.1-0.7 mmol/kg/day.

Other Non-Primate Mammals

[PubMed]

At 0.1 mmol/kg i.v. doses in dogs, Gd-DTPA-BMEA did not appear to cause any toxic or cardiovascular effect (14, 16). At doses of 0.3-1.0 mmol/kg, dose-related decreases in both blood pressure and left ventricular systolic pressure were observed. At higher doses of 0.6-3.0 mmol/kg, abnormal effects were observed in body weights, kidneys, and hematologic parameters. No *in utero* survival and fetal development effect was observed in rabbits at doses of 0.1-0.4 mmol/kg/day.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Swan and colleagues (17) conducted a double-blind, randomized, placebo-controlled, parallel-group, multicenter (10 sites) study of 121 subjects who received 0.1-0.5 mmol/kg of Gd-DTPA-BMEA. It was distributed in the extracellular fluid and eliminated primarily in urine, after 72 h, with a mean range from 80% of total excreted activity for the dose of 0.1 mmol/kg to 85% for the dose of 0.5 mmol/kg. This rate appeared to be consistent with renal elimination through glomerular filtration, and elimination was delayed by a decrease in renal function. The normal elimination rate constants (k_{el}s) ranged from 0.415 to 0.357 h^{-1} (0.1-0.5 mmol/kg) were decreased to lower rate constants from 0.091 to 0.121 h^{-1} for patients with renal insufficiency. At the doses tested in the study, Gd-DTPA-BMEA appeared to have no adverse effect on kidney function, and no significant changes were observed in patients with CNS or liver pathology. In another study with healthy pedi-

atric subjects (*n* = 17) who received a single i.v. dose of 0.1 mmol/kg of Gd-DTPA-BMEA, the younger group (from 2 to <5 years of age) had a slight but significantly (P<0.05) shorter mean elimination ($t_{½}$) of 1.19 h than the 1.39 h of the older group (from 5 to <18 years of age) (2).

A 2002 publication summarized the safety data of Gd-DTPA-BMEA from 1663 injections that indicated a similar safety profile with an adverse event ratio (overall adverse events divided by the number of subjects) of 1.95 events/subject as compared with 3.68 events/subject for placebo (*n* = 46) (3). At the 0.1 mmol/kg i.v. dose of Gd-DTPA-BMEA, the overall adverse event rate was 29.3% (*n* = 959) and was comparable to 34.7% (*n* = 329) of Gd-DTPA. Other studies showed that Gd-DTPA-BMEA had a similar clinical efficacy profile when compared with other commercially available MRI contrast agents [PubMed].

References

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